

## OUTCOME OF TREATMENT IN CHILDREN WITH PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

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### ABSTRACT

**Background** Children with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL) have a poor prognosis, and there is no consensus on the optimal treatment for this variant of ALL.

**Methods** We reviewed the medical records of patients with Ph-positive ALL who were treated with intensive chemotherapy, with or without bone marrow transplantation, by 10 study groups or large single institutions from 1986 to 1996. Data on 326 children and young adults, who ranged in age from 0.4 to 19.9 years (median, 8.1), were analyzed to determine the rate of complete remission and the probability of event-free, disease-free, and overall survival according to standard prognostic factors and type of treatment.

**Results** The 267 patients who had a complete remission after induction chemotherapy (82 percent) were stratified into three subgroups according to the age and leukocyte count at the time of diagnosis: those with the best prognosis (a leukocyte count of less than 50,000 per cubic millimeter and an age of less than 10 years; 95 patients); those with an intermediate prognosis (intermediate-risk features; 92 patients); and those with the worst prognosis (a leukocyte count of more than 100,000 per cubic millimeter; 80 patients). The estimates of disease-free survival at five years ( $\pm$ SE) were  $49\pm 5$  percent (for patients with the best prognosis),  $30\pm 5$  percent (for those with an intermediate prognosis), and  $20\pm 5$  percent (for those with the worst prognosis) ( $P < 0.001$  for the overall comparison). We also found that transplantation of bone marrow from an HLA-matched related donor offered significantly greater benefit than intensive chemotherapy alone in terms of protecting patients from relapse or other adverse events (relative risk, 0.3; 95 percent confidence interval, 0.2 to 0.5;  $P < 0.001$ ). This finding was consistent in all three subgroups.

**Conclusions** Unlike the usual type of ALL, Ph-positive ALL is associated with a poor prognosis. Nevertheless, in some patients with favorable prognostic features, the disease can be controlled by intensive chemotherapy. Transplantation of bone marrow from an HLA-matched related donor is superior to other types of transplantation and to intensive chemotherapy alone in prolonging initial complete remissions. (N Engl J Med 2000;342:998-1006.)

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**T**HE probability of curing childhood acute lymphoblastic leukemia (ALL) with current treatments ranges from 75 percent to 80 percent. Although some adverse prognostic features have lost clinical importance with recent improvements in therapy,<sup>1</sup> other such features remain associated with worse outcomes. These include a very high leukocyte count at diagnosis,<sup>2</sup> the presence of more than 1000 leukemic cells per cubic millimeter one week after preliminary treatment with glucocorticoids and intrathecal methotrexate,<sup>3</sup> and the failure of a full course of induction therapy to induce a complete remission. Several different molecular genetic abnormalities can also confer a poor prognosis<sup>4</sup>; of these, the chromosomal translocation t(9;22) is associated with the worst outcome in childhood ALL.

The translocation t(9;22), which generates the Philadelphia chromosome (Ph), occurs in 3 to 5 percent of children with ALL,<sup>5</sup> as compared with about 25 percent of adults with the disease. The translocation can result in a fusion protein of 210 kd (p210) when the *abl* proto-oncogene moves from chromosome 9 to the major breakpoint cluster region on chromosome 22. This is the usual finding in chronic myelogenous leukemia and occurs occasionally in Ph-positive ALL. The *abl* gene can also translocate to the minor breakpoint cluster region on chromosome 22, resulting in

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a 190-kd fusion protein (p190) that occurs exclusively in ALL. More than 90 percent of children with Ph-positive ALL have this subtype of t(9;22).<sup>6</sup> Both the p210 and p190 proteins are readily detected with techniques based on the polymerase chain reaction (PCR).<sup>5-8</sup>

Overall, Ph-positive ALL has a dire prognosis (rates of event-free survival are 25 to 30 percent in children and less than 20 percent in adults).<sup>9-21</sup> However, some investigators suggest that in this type of ALL, the prognosis is influenced by the outcome of treatment with glucocorticoids (and intrathecal methotrexate), which are given before induction chemotherapy is instituted,<sup>22</sup> or by other factors (such as age and leukocyte count at diagnosis) in children treated only with intensive chemotherapy.<sup>16,19-22</sup> These variations in the response to therapy suggest that Ph-positive ALL is heterogeneous with regard to sensitivity to treatment. To test this idea, we collected and centrally reviewed the medical records of 326 children and young adults with Ph-positive ALL who were treated by 10 participating cooperative groups or large single institutions in Europe and the United States. Our main objectives were to identify prognostically important subgroups of patients and to assess the effect of different post-remission therapies on disease-free and overall survival.

## METHODS

### Review of Data

Each study group reviewed its own records to identify patients with Ph-positive ALL who were registered in clinical trials between 1986 and 1996. We accepted either cytogenetic or molecular criteria for identification of the Philadelphia chromosome; patients who were negative for the chromosome at diagnosis but positive at relapse were not included. A predefined set of data, collected for each patient, was then sent to a central coordinating center, where the findings were reviewed for consistency and completeness. Follow-up observations extended through 1999, with a median follow-up of 7.3 years. By general agreement, none of the participating groups are identified with their data sets in this report.

### Patients and Treatment

A total of 326 patients with Ph-positive childhood ALL were identified. At most of the participating centers, these children were identified early in the clinical course and were promptly assigned to therapy for high-risk ALL. Of the 289 patients for whom risk-group assignment could be evaluated, 242 (84 percent) were treated with one of the high-risk protocols used by the participating centers. Indications for bone marrow transplantation for patients in first complete remission varied among the different study groups. Nonetheless, transplantation of bone marrow from an HLA-matched related donor was generally accorded the highest priority among alternatives to chemotherapy alone. The lack of information on the availability of donors prevented us from determining whether all patients with a suitable donor underwent allogeneic transplantation.

### Statistical Analysis

The principal end points in the analysis of treatment results were event-free survival, disease-free survival, and overall survival. Event-free survival was defined as the time from diagnosis to a first adverse event: death during induction therapy, lack of achievement of remission during the protocol-specified induction period, relapse at

any site, death during remission, or the development of a second neoplasm. Disease-free survival was defined as the time from complete remission until relapse at any site, death during complete remission, or the development of a second neoplasm. Survival was defined as the time from diagnosis to death from any cause. Observations on patients without adverse events were censored as of the date of last contact, which occurred during 1999 for all but 30 patients, whose follow-up times extended through 1997 or 1998. The Kaplan-Meier method was used to estimate the probabilities of disease-free survival and overall survival, with standard errors calculated according to the method of Greenwood. Curves were compared by means of the log-rank test. The annual rate of relapse was estimated by means of the actuarial estimator.

Statistical methods were used to minimize potential sources of bias in comparisons of different types of bone marrow transplantation with intensive chemotherapy alone.<sup>23</sup> In these analyses, disease-free survival was calculated from the date of diagnosis. Differences in time to transplantation and in the prognostic factors used to assign patients to this procedure were accounted for in Cox regression analyses. Treatment was considered to be a time-dependent factor. Thus, each patient was included in the chemotherapy-only group until transplantation, at which point he or she was shifted to the specific transplantation group under study or data were censored for other types of transplantation. The model also included the covariates age (younger than 10 years vs. 10 years or older), leukocyte count at presentation (less than 50,000, 50,000 to 100,000, or more than 100,000 per cubic millimeter), and sex or the modified Rome-National Cancer Institute determinants of prognostic subgroups in childhood ALL, which combine the effects of age and leukocyte count to identify subgroups with different prognoses.<sup>2,24</sup> No substantial departures from the proportional-hazards assumption emerged from graphical checks on the prognostic factors.

The time dependence of the treatment effect was accommodated by including a term for the interaction of time and treatment in the regression analysis. Two-tailed P values for differences in the risk of treatment failure (in terms of either disease-free survival or overall survival) were derived from the likelihood-ratio test. Estimated hazard ratios are reported as relative risks with 95 percent confidence intervals. Kaplan-Meier plots that compared transplantation of bone marrow from a matched related donor with chemotherapy alone were adjusted to account for the waiting time to transplantation.<sup>25</sup> Thus, the curves originate at the median time to transplantation and do not include patients who had adverse events or whose data were censored before that time. P values refer to the Mantel-Byar test. A modified Mantel-Byar test for the univariate comparison of survival times<sup>26</sup> yielded similar results when applied to the same data set (data not shown).

## RESULTS

### Clinical and Laboratory Characteristics

The Philadelphia chromosome was identified by cytogenetic analysis in 320 patients and by molecular analysis in the remaining 6. Table 1 summarizes the presenting features of the patients. The usual excess number of boys (approximately 52 percent of patients) in representative groups of patients with childhood ALL was more pronounced in this series (64 percent). The median age at diagnosis was 8.1 years (range, 0.4 to 19.9). Of the 326 patients, 37 (11 percent) were less than two years of age; only 1 patient was younger than one year of age. The leukocyte count at the time of diagnosis was at least 50,000 per cubic millimeter in approximately half the patients and less than 10,000 per cubic millimeter in 21 percent. Seventy-five percent of the patients had a platelet count of more than 27,000 per cubic millimeter and

**TABLE 1.** PRESENTING FEATURES OF 326 PATIENTS WITH Ph-POSITIVE CHILDHOOD ALL, ACCORDING TO THE RESPONSE TO INDUCTION THERAPY AND CATEGORY OF POST-REMISSION THERAPY.

CHARACTERISTIC	NO RESPONSE TO INDUCTION THERAPY (N=59)	REMISSION		ALL PATIENTS (N=326)
		CHEMOTHERAPY ONLY (N=147)	BONE MARROW TRANSPLANTATION (N=120)	
Year of diagnosis — no. (%)				
1986–1988	13	42	8	63 (19)
1989–1991	14	53	36	103 (32)
1992–1994	24	37	63	124 (38)
1995–1996*	8	15	13	36 (11)
Male sex — no. (%)	42	91	77	210 (64)
Age				
25th, 50th, and 75th percentiles — yr				4.5, 8.1, 12.1
Median — yr	10.8	7.5	6.9	
0–2 yr — no. (%)†	5	17	15	37 (11)
3–5 yr — no. (%)	8	42	33	83 (25)
6–9 yr — no. (%)	12	35	34	81 (25)
10–14 yr — no. (%)	29	42	28	99 (30)
≥15 yr — no. (%)	5	11	10	26 (8)
White-cell count at diagnosis				
25th, 50th, and 75th percentiles — per mm <sup>3</sup>				12,000, 48,000, 137,000
Median — per mm <sup>3</sup>	132,000	40,000	31,400	
<10,000 — no. (%)	6	33	29	68 (21)
10,000 to <25,000 — no. (%)	7	28	24	59 (18)
25,000 to <50,000 — no. (%)	4	13	20	37 (11)
50,000 to <100,000 — no. (%)	8	23	17	48 (15)
≥100,000 — no. (%)	34	50	30	114 (35)
Platelet count — per mm <sup>3</sup> ‡				
25th, 50th, and 75th percentiles				27,000, 58,000, 127,000
Median	60,000	52,000	60,000	
Hemoglobin — g/dl§				
25th, 50th, and 75th percentiles				6.3, 8.7, 11.0
Median	9.7	8.7	8.7	
Immunophenotype — no. (%)¶				
B lineage	51	137	112	300 (98)
T lineage	1	3	2	6 (2)
Involvement of central nervous system — no. (%)	2	4	5	11 (4)
Response to glucocorticoid plus intra- thecal methotrexate — no. (%)**				
Poor (≥1000 blasts/mm <sup>3</sup> on day 8)	15	4	3	22 (28)
Good (<1000 blasts/mm <sup>3</sup> on day 8)	5	23	30	58 (72)

\*Two study groups did not contribute patients after 1994.

†Only one patient was younger than one year of age.

‡Data on platelet count were available for 280 patients.

§Data on hemoglobin were available for 257 patients.

¶Data on immunophenotype were available for 306 patients.

||Data on involvement of the central nervous system were available for 282 patients.

\*\*Data on response to glucocorticoid plus intrathecal methotrexate were available for 80 patients.

a hemoglobin level higher than 6.3 g per deciliter. The leukemic cells had a B-cell–lineage immunophenotype in 98 percent of the cases (in 211 of the 221 cases tested [95 percent], they bore the CD10 antigen). Despite the relatively high proportion of patients with hyperleukocytosis, leukemic involvement of the central nervous system at diagnosis was rare (4 percent).

#### Early Responses to Chemotherapy

By protocol design, early responses to treatment were evaluated in 130 patients. In the subgroup of 80 patients in whom we assessed the response to preliminary treatment with glucocorticoids and intrathecal methotrexate,<sup>3</sup> 72 percent were considered to have had a good response (<1000 blasts per cubic millimeter in peripheral blood after seven days of glucocorticoid

**TABLE 2.** PATTERNS OF TREATMENT FAILURE IN 267 PATIENTS WITH Ph-POSITIVE CHILDHOOD ALL WHO HAD COMPLETE RESPONSES TO INITIAL INDUCTION THERAPY.

CHARACTERISTIC	CHEMOTHERAPY ONLY (N=147)*	BONE MARROW TRANSPLANTATION					ALL PATIENTS (N=267)
		MATCHED RELATED DONOR (N=38)	MATCHED UNRELATED DONOR (N=21)†	MISMATCHED RELATED DONOR (N=16)	AUTOLOGOUS (N=25)	ALLOGENEIC‡	
Time from diagnosis to transplantation — mo							
Median	NA	6	10	8	7	3	6.6
Range	NA	3–32	3–29	3–18	4–24	2–18	2–32
Relapse — no. (%)	113	9	4	1	14	3	144 (54)
In bone marrow	92	8	3	0	11	2	116
In central nervous system	13	1	0	0	1	1	16
In testis	3	0	0	1	0	0	4
In bone marrow and other site or sites	5	0	1	0	2	0	8
Death during continuous complete remission — no. (%)	8	3	9	7	3	5	35 (13)
Related to bone marrow transplantation	NA	3	7	2	1	1	14
Related to infection	4	0	1	3	2	1	11
Related to other factors	4	0	1	2	0	3	10
Second malignant neoplasms — no. (%)	2§	0	0	1¶	2	0	5 (2)
Continuous complete remission — no. (%)	24	26	8	7	6	12	83 (31)

\*NA denotes not applicable.

†This group also included one patient who received a transplant from a mismatched unrelated donor.

‡Allogeneic bone marrow transplants were not further defined.

§In one patient, acute myeloid leukemia developed 3.5 years after the diagnosis of ALL, and in the other, a new ALL with a different genotype developed 6 years after diagnosis of ALL.

¶Glioma developed 5.9 years after transplantation.

||In one patient, astrocytoma developed 4.8 years after transplantation, and in the other, chronic myelogenous leukemia developed 7 years after transplantation.

therapy and one injection of intrathecal methotrexate), and 28 percent had a poor response, a proportion more than twice that in groups of unselected patients with ALL.<sup>16,27,28</sup> Of 18 patients who were evaluated for a response in the blood count after seven days of multiagent chemotherapy,<sup>29</sup> 5 (28 percent) had a blast-cell count of more than 1000 per cubic millimeter. Bone marrow aspirates were evaluated at seven days in 28 patients, 13 of whom (46 percent) had more than 25 percent blast cells in the marrow, a proportion considerably higher than that in unselected patients with childhood ALL.<sup>30,31</sup>

**Induction of Complete Remission**

Of the 326 patients in the study, 267 (82 percent) entered a complete remission a median of 31 days after diagnosis. Of the 59 patients with incomplete responses to induction chemotherapy, 3 died of treatment-related complications and 56 had resistant leukemia. As compared with patients who entered remission, these 59 patients tended to be older, were more likely to be male, had higher leukocyte counts, and had a poorer response to glucocorticoids plus intrathecal methotrexate (Table 1). Complete remissions were subsequently induced a median of 80 days after diagnosis (range, 41 to 190) in 26 of the 56 patients who had a poor response to the first round of induction chemotherapy and who could be evaluated. Later

adverse events in this subgroup included 16 relapses and 7 deaths while the patient was in complete remission. Of the 26 patients who eventually had a remission, 3 remained in remission for 9.3, 8.7, and 4.3 years, respectively, after they received a bone marrow transplant from a matched related donor (2 patients) or a mismatched related donor (1 patient). Of the 18 remaining patients whose disease remained refractory to chemotherapy, 17 died a median of 0.9 year after diagnosis (5 of whom died despite receiving a transplant during partial remission); 1 child, who received a transplant from a matched related donor, was alive 8 years after diagnosis. Of the 12 patients for whom there was no information concerning later remission and subsequent therapy, 11 died a median of 1.1 years after diagnosis, and 1 was alive at 7 years.

**Patterns of Treatment Failure**

Of the 267 patients who had a complete remission after the initial phase of induction chemotherapy, 144 had a relapse: 116 in the bone marrow (81 percent), 16 in the central nervous system (11 percent), 8 in bone marrow and another site or sites (6 percent), and 4 in the testis (among 168 boys) (Table 2). In addition, 35 of these 267 patients (13 percent) died during the first remission, a median of 1.2 years (range, 0.2 to 5.7) after remission was induced. The cause of death was related to bone marrow transplantation in

14 patients, infection in 11, and other factors in 10. Second malignant neoplasms developed in five patients (2 percent) as the first adverse event. Altogether, 83 of the 267 patients (31 percent) were in continuous complete remission on the date of the last evaluation.

#### Factors That Influenced Event-free, Disease-free, and Overall Survival

The estimates of event-free survival and overall survival ( $\pm$ SE) five years after diagnosis in the combined study group were  $28\pm 3$  percent and  $40\pm 3$  percent, respectively. At seven years they were  $25\pm 3$  percent and  $36\pm 3$  percent, respectively. An analysis of prognostic factors based on the characteristics of all 326 patients in the study showed that age, initial leukocyte count, and response to initial treatment with glucocorticoids and intrathecal methotrexate had a significant effect on the outcome of treatment (Table 3). Regarding the last factor, only 7 of the 22 patients with a poor response to glucocorticoids and intra-

thecal methotrexate (32 percent) had a complete remission, and in that group, only 2 patients were alive at last follow-up (8 years for 1 patient and 9.7 years for 1 patient); in this subgroup, the event-free survival was zero within 2 years after diagnosis. In contrast, 53 of 58 patients who had a good response to glucocorticoids and intrathecal methotrexate (91 percent) had a complete remission, with an estimated event-free survival at five years of  $39\pm 7$  percent.

To identify subgroups that differed according to prognosis, we stratified the group of 267 patients with a complete response according to age and leukocyte count at the time of diagnosis,<sup>2,24</sup> regardless of the treatment outcome. The resulting three subgroups, defined as those with the worst, intermediate, and best prognoses, were similar in size (80, 92, and 95 patients, respectively) and had significantly different rates of disease-free survival at five years:  $20\pm 5$  percent (worst),  $30\pm 5$  percent (intermediate), and  $49\pm 5$  percent (best) ( $P<0.001$  for the overall comparison) (Fig. 1). Each of these subgroups was represented in the population of 194 patients who had complete responses to induction therapy designed for high-risk patients, whereas the patients who had complete responses to induction therapy that was not designed for high-risk patients were virtually all from the best-prognosis subgroup.

To assess the effect of different post-remission treatments on disease-free survival and overall survival, we used a Cox regression model adjusted for time to bone marrow transplantation, initial leukocyte count, age, and sex. As compared with the group treated with chemotherapy alone, patients who underwent transplantation of bone marrow from a matched related donor had a significantly lower risk of treatment failure: relative risk of death or adverse events, 0.3 (95 percent confidence interval, 0.2 to 0.5;  $P<0.001$ ), and relative risk for death from any cause, 0.4 (95 percent confidence interval, 0.2 to 0.7;  $P=0.002$ ) (Table 4). The advantage of transplantation of bone marrow from matched related donors became more apparent with each successive year of follow-up (Fig. 2), suggesting greater protection against late relapses than with chemotherapy alone in patients who survived the early toxic effects of treatment. None of the other types of bone marrow transplantation had any therapeutic advantage over chemotherapy alone (Table 4). The superiority of marrow transplantation from a matched related donor extended to each of the prognostic subgroups identified with the modified Rome–National Cancer Institute criteria.<sup>2,24</sup> The  $P$  values for the interaction between treatment and prognostic subgroup were 0.48 for disease-free survival and 0.73 for overall survival. In the subgroup with the best prognosis, the relative risk of death or adverse events was 0.2 (95 percent confidence interval, 0.04 to 0.7) and that of death from any cause was 0.3 (95 percent confidence interval, 0.1 to 1.1). Among

**TABLE 3.** RATES OF EVENT-FREE SURVIVAL AND OVERALL SURVIVAL ACCORDING TO THE PRESENTING FEATURES OF 326 PATIENTS WITH Ph-POSITIVE CHILDHOOD ALL.\*

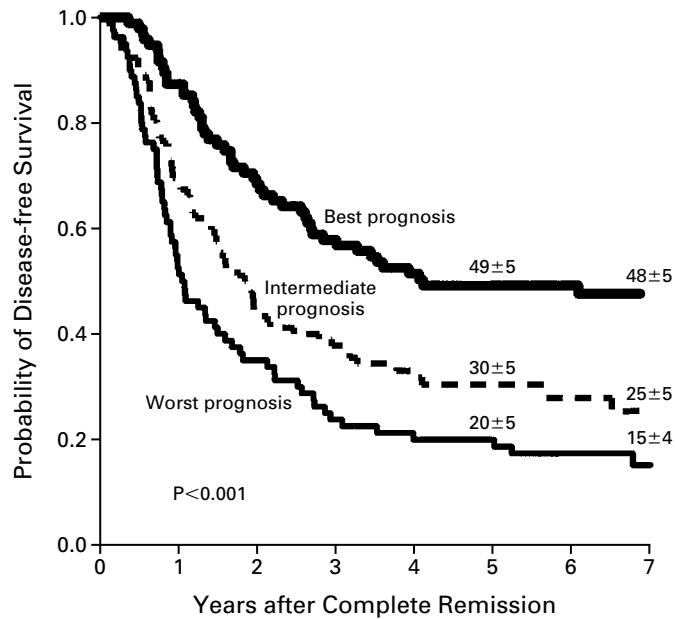
CHARACTERISTIC	5-Yr EVENT-FREE SURVIVAL	P VALUE	5-Yr OVERALL SURVIVAL	P VALUE
	%		%	
Year of diagnosis		0.21		0.47
1986–1988	21 $\pm$ 5		32 $\pm$ 6	
1989–1991	24 $\pm$ 4		42 $\pm$ 5	
1992–1994	35 $\pm$ 4		43 $\pm$ 5	
1995–1996†	—		—	
Sex		0.12		0.11
Male	26 $\pm$ 3		38 $\pm$ 3	
Female	32 $\pm$ 4		44 $\pm$ 5	
Age		0.001		0.007
0–2 yr	38 $\pm$ 8		54 $\pm$ 8	
3–5 yr	32 $\pm$ 5		42 $\pm$ 6	
6–9 yr	33 $\pm$ 5		47 $\pm$ 6	
10–14 yr	18 $\pm$ 4		30 $\pm$ 5	
$\geq$ 15 yr	21 $\pm$ 8		29 $\pm$ 9	
White-cell count at diagnosis (per mm <sup>3</sup> )		<0.001		<0.001
<10,000	40 $\pm$ 6		51 $\pm$ 6	
10,000 to <25,000	42 $\pm$ 6		53 $\pm$ 7	
25,000 to <50,000	30 $\pm$ 8		35 $\pm$ 8	
50,000 to <100,000	25 $\pm$ 7		42 $\pm$ 7	
$\geq$ 100,000	14 $\pm$ 3		27 $\pm$ 4	
Response to glucocorticoid plus intrathecal methotrexate		<0.001		<0.001
Poor (at 1 yr)‡	9 $\pm$ 6		59 $\pm$ 11	
Good (at 1 yr)§	74 $\pm$ 6		86 $\pm$ 5	

\*Plus–minus values are standard errors.  $P$  values are from the log-rank test. For year of diagnosis only,  $P$  values are for trend.

†The sample size was too small for the Kaplan–Meier analysis.

‡Data were available for 22 patients. At five years, the rate of event-free survival was 0 percent.

§Data were available for 58 patients. At five years, the rate of event-free survival was  $39\pm 7$  percent and the rate of overall survival was  $55\pm 7$  percent.



PATIENTS AT RISK								
Best prognosis	95	83	65	55	46	39	32	22
Intermediate prognosis	92	64	40	33	25	14	11	9
Worst prognosis	80	42	28	19	16	15	10	5

**Figure 1.** Estimates of Disease-free Survival ( $\pm$ SE) in 267 Patients with Ph-Positive Childhood ALL. The patients were classified according to modified Rome–National Cancer Institute criteria, as follows: best prognosis (10 years of age or younger with a leukocyte count of less than 50,000 per cubic millimeter), intermediate prognosis (intermediate-risk features), and worst prognosis (any age with a leukocyte count of more than 100,000 per cubic millimeter). Five-year and seven-year estimates are shown.  $P < 0.001$  by the log-rank test for overall comparison of outcome in the three prognostic subgroups.

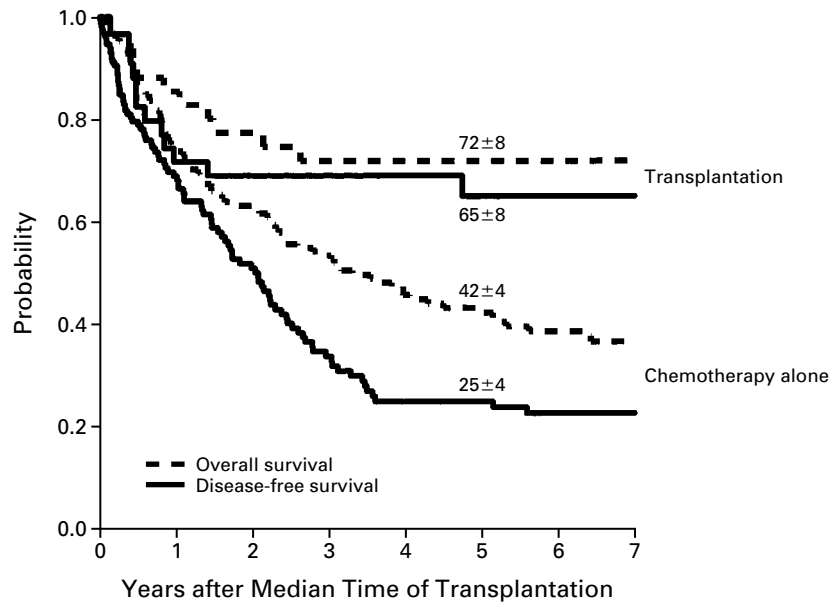
**TABLE 4.** ESTIMATED RELATIVE RISKS ASSOCIATED WITH DIFFERENT TYPES OF BONE MARROW TRANSPLANTATION AND CHEMOTHERAPY ALONE IN 267 PATIENTS WITH Ph-POSITIVE CHILDHOOD ALL WHO HAD COMPLETE RESPONSES TO INITIAL INDUCTION THERAPY.\*

TREATMENT	NO. OF PATIENTS IN WHOM TREATMENT FAILED/TOTAL NO. OF PATIENTS†	DISEASE-FREE SURVIVAL	P VALUE	OVERALL SURVIVAL	P VALUE
		RR (95% CI)		RR (95% CI)	
Chemotherapy alone	123/147	1.0		1.0	
<b>Bone marrow transplantation</b>					
Autologous	19/25	1.1 (0.7–1.8)	0.66	1.2 (0.7–2.0)	0.48
Matched unrelated donor	13/21	1.3 (0.7–2.4)	0.40	1.4 (0.8–2.6)	0.26
Mismatched related donor	9/16	0.8 (0.4–1.5)	0.45	0.8 (0.5–1.4)	0.57
Matched related donor	12/38	0.3 (0.2–0.5)	<0.001	0.4 (0.2–0.7)	0.002
Matched related donor‡	12/38				
At 1 yr		0.5 (0.3–1.0)		0.5 (0.3–1.5)	
At 2 yr		0.3 (0.1–0.9)		0.3 (0.1–1.2)	
At 3 yr		0.1 (0.02–0.8)		0.2 (0.03–1.3)	

\*Shown are results from a Cox regression model adjusted for leukocyte count, age, and sex with correction for waiting time to bone marrow transplantation. For disease-free survival, the relative risk (RR) is of death or adverse events; for overall survival, the relative risk is of death from any cause. The reference group was the patients who received chemotherapy alone. CI denotes confidence interval.

†These numbers include relapses, deaths, and second malignant neoplasms.

‡This additional model includes a term for evaluating the change in the relative risk over time; the coefficient for the interaction between treatment and time was significantly different from 1 for disease-free survival only ( $P = 0.02$ ).



PATIENTS AT RISK		0	1	2	3	4	5	6	7
Chemotherapy alone		198	84	57	36	24	22	18	14
Transplantation from matched related donor		18	28	25	26	23	17	9	6

**Figure 2.** Estimates of Disease-free and Overall Survival ( $\pm$ SE) in 267 Patients Treated with Transplantation of Bone Marrow from HLA-Matched Related Donors or Chemotherapy Only.

The curves have been adjusted for waiting time to transplantation, so that the zero on the time axis corresponds to the median time from diagnosis to transplantation (six months); patients were assigned to this treatment group in a time-dependent fashion. Five-year estimates are shown. P values are from the Mantel–Byar test. P=0.002 for the comparison of the two treatments with respect to overall survival; P<0.001 for the comparison with respect to disease-free survival.

patients with an intermediate prognosis, these relative risks were 0.5 (95 percent confidence interval, 0.3 to 0.98) and 0.6 (95 percent confidence interval, 0.2 to 1.6), respectively, and among those with a poor prognosis, they were 0.3 (95 percent confidence interval, 0.1 to 0.8) and 0.4 (95 percent confidence interval, 0.1 to 1.1).

### DISCUSSION

Recent advances in treatment have increased the rate of cure of childhood ALL to 75 percent or better.<sup>32</sup> However, attempts to improve results for resistant subtypes of ALL, such as ALL in patients with the Philadelphia chromosome, have been largely unsuccessful. Much of the difficulty can be traced to the lack of a large enough number of patients with this subtype, which is needed to ensure statistically valid analyses in retrospective studies or prospective investigations of new treatments. For this reason, we reviewed documented cases of Ph-positive ALL that were diagnosed and treated by 10 study groups or large single institutions from 1986 to 1996. We identified 326 patients who met all our criteria for inclusion in the study reported here.

The poor prognosis for patients with Ph-positive ALL is due partly to the relatively slow rate of reduction of the leukemic clone by chemotherapy, as indicated by the persistence of circulating blast cells after initial glucocorticoid therapy or of a high proportion of blasts in the marrow eight days after the initiation of induction chemotherapy.<sup>22,29-31</sup> We found that 18 percent of the patients in our study did not enter remission by the end of the specified induction period, a rate that is much worse than the 2 to 3 percent failure rate in series of unselected patients with childhood ALL.<sup>16,17,27,28,31-35</sup> About one half of the patients in whom induction therapy failed entered remission with further chemotherapy, but most of them ultimately relapsed, underscoring the dire prognosis for patients with blast cells that resist initial therapy. Nevertheless, the occasional induction of a durable second remission in patients who relapse after initial chemotherapy warrants repeated courses of intensive chemotherapy, with or without bone marrow transplantation, for any child with initially resistant disease.

Relapse was the most common cause of treatment failure in our series. About half the patients who en-

tered remission had a relapse, mainly in the bone marrow. As expected, the relapse rate was highest early in the course of treatment (28 relapses per 100 person-years during the first year, and 24 during the second). In contrast to the rates in other subgroups of patients with high-risk ALL, the relapse rate in children with Ph-positive ALL remained high during the third and fourth years (18 and 14 relapses per 100 person-years). Thus, at least four years of observation may be required to determine the efficacy of new treatments for Ph-positive ALL.

Most leukemia specialists would recommend bone marrow transplantation for a child with Ph-positive ALL in first remission,<sup>36</sup> but the advantage of this strategy has not been demonstrated in a large-scale clinical study. Using statistical methods to correct for delays in transplantation that could bias the evaluation of efficacy, we found that transplantation of marrow from an HLA-matched related donor yields a significantly better outcome in Ph-positive patients than chemotherapy alone. This type of transplantation, undertaken a median of six months after diagnosis, caused few deaths and markedly reduced the rate of leukemic relapse (Table 4 and Fig. 2). Similar analyses are not available for adults with Ph-positive ALL, although a report from the International Bone Marrow Transplantation Registry indicates an improved rate of leukemia-free survival in adult patients who received a marrow transplant from an HLA-identical sibling.<sup>37</sup>

The fact that most patients who are eligible for bone marrow transplantation lack a matched related donor forces physicians to consider alternative sources of hematopoietic stem cells. In this study, transplantation of marrow from a mismatched related donor or of autologous marrow was not superior to chemotherapy alone. Because of an excess number of transplantation-related deaths (Table 2), the group that received marrow from matched unrelated donors had a risk of treatment failure that was higher than (although not significantly higher than) that in the group treated with chemotherapy alone (Table 4). This result supports our opinion that transplantation of marrow from a matched unrelated donor should be undertaken only in centers where the results of this procedure are similar to those obtained with matched related donors. Indications for the use of alternative donors should be continuously updated in the light of progress in both the prevention of transplantation-related toxicity<sup>38,39</sup> and the efficacy of chemotherapy for high-risk patients.<sup>40</sup> We advise caution in using treatments that produce encouraging short-term results but lack long-term evaluation.

We conclude that Ph-positive ALL is a heterogeneous disease with respect to treatment outcome. Among patients with this variant of ALL who presented with leukocyte counts higher than 100,000 per cubic millimeter, 85 percent did not have long-term disease-free survival. The inadequacy of current ther-

apy for such patients, most of whom can be readily identified by their initial response to prednisone, indicates a need for new treatments. Patients with Ph-positive ALL who are younger than 10 years old and have a leukocyte count of less than 50,000 per cubic millimeter at the time of diagnosis have about a 50 percent chance of long-term disease-free survival, whereas the remaining patients (those with a leukocyte count of 50,000 to 100,000 per cubic millimeter and those with less than 50,000 leukocytes per cubic millimeter who are older than 10 years of age) have an intermediate prognosis (estimate of five-year disease-free survival, 30 percent). The fact that the results of initial glucocorticoid therapy (plus intrathecal methotrexate) are so useful in discriminating between patients with a good prognosis and those with a poor one should be exploited as often as possible in assigning patients with Ph-positive ALL to specific treatment groups (Table 3). Further cooperation among leukemia specialists worldwide will be needed to generate and test relevant hypotheses pertaining to Ph-positive ALL and other uncommon subtypes of acute leukemia.<sup>41,42</sup>

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